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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,713	SCHENK, DALE B.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,56-59,61 and 63-128* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33, 56-59, 61, 63-128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed on 3/24/04 has been entered. Applicant's amendment canceled claims 34, 60, and 62, and added new claims 68-128. Therefore, claims 33, 56-59, 61, and 63-128 are pending and under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of claims 33-34 and 56-67 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as claimed, is maintained in part. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

Regarding the grounds of rejection concerning the lack of enabling disclosure for chimeric, humanized, or human antibody chains comprising only a heavy or light chain, the use of a single heavy or light chain gene or protein to bind to an epitope within Aβ1-10, or the use of polynucleotide that is not DNA operatively linked to transcription control elements, it is noted that the amendments to the claims have overcome this aspect of the rejection.

Regarding the remaining grounds of rejection, the applicant argues that the unpredictability associated with gene therapy as a whole as evidenced by Verma et al., Marshall et al., Eck et al., and Orkin et al. does not apply to the instant invention since the presently claimed methods are an undemanding form of gene therapy which require only transient accumulation of antibody in the blood. The applicant also argues that the problems identified in the cited references were already largely solved by 1997 including problems with different vectors and promoter selection. In addition, the applicant states that while FDA approval is not a standard for patentability, over 800 clinical trials involving gene therapy have been approved.

In response, while it is true that Verma et al. does provide some examples of progress in treating disease using direct gene transfer, Verma et al. still concludes that as of 1997 the practice of therapeutic gene expression for treating disease is plagued by problems including problems specific to different vector types, and general problems with levels of gene expression and exposure of the gene product to the target tissue. Marshall et al. also discusses advances in therapeutic gene transfer; however, based on all the evidence, Marshall summarizes the prospects for predictable gene therapy of disease as , "many problems must be solved before gene therapy will be useful for more than the **rare** application" (Marshall et al. (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1, emphasis added). Orkin et al. was also cited in the previous office action and again while discussing some rare successes and advances in gene transfer technology, clearly states, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of

these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4, and page 8, paragraph 2). Eck et al. concurs with the conclusions of Verma, Marshall, and Orkin. Eck et al. reports that despite numerous clinical trials in progress, gene therapy is still in its infancy. While all the cited references agree that therapeutic gene transfer has potential and that advances in gene transfer technology will likely occur, at the time of filing, the state of the art of therapeutic gene transfer to treat disease was unpredictable.

Based on the level of unpredictability in the art at the time of filing, the onus is on the specification to provide the missing disclosure for achieving successful treatment or prophylaxis of diseases characterized by amyloid plaques comprising Aβ peptide using DNA encoding antibodies which bind to an epitope in Aβ1–10 . However, as discussed in detail in the previous office actions, the specification fails to provide the requisite teachings to enable the practice of the scope of the invention as claimed. The specification is primarily directed to immunization with Aβ peptides or with the passive transfer of monoclonal protein antibodies. The specifications teachings regarding the delivery of DNA encoding an antibody which binds to an epitope within Aβ1-10 are limited to a brief and general description of gene transfer and vectors on page 25 of the specification and are entirely prophetic. The specification provides no specific guidance as to particular vectors which are in fact capable of expressing sufficient levels of any encoded antibody over multiple administrations resulting in treatment of diseases such as Alzheimer's disease. Based on the combined teachings of Marshall et al., Eck et al., Verma et al., and Orkin et al., it is clear that more is required to predict success since all the vector systems

listed on page 25 suffer from limitations that undermine their therapeutic usefulness. Furthermore, the specification provides no guidance as to any nucleic acid sequences encoding any antibody which binds to an epitope within Aβ1-10 or within Aβ1-5 whose expression in the blood or any other location in the body at any level or duration or expression would be sufficient to reduce or prevent amyloid plaques or plaque formation. The closest evidence provided by the specification concerns the passive administration of protein antibodies. However, this evidence of record demonstrates further complicates the issue since the evidence demonstrates that even with direct administration of protein antibody which binds to an epitope within Aβ1-10, therapeutic efficacy is not predictable. Example XI shows that administration of the 2H3 antibody directed against an epitope within Aβ1-12 was ineffective in preventing or ameliorating plaque deposits in transgenic mice due to problems with rapid antibody clearance. Of the antibodies tested only the 10D5 antibody showed any statistically significant effect. Thus, even following direct protein antibody administration, the treatment of amyloid plaques with antibodies that bind to an epitope within Aβ1-10 is not predictable. Therefore, based on the art-recognized unpredictability of achieving therapeutic levels of gene expression using currently available vectors at the time of filing, the unpredictability in treating or preventing amyloid plaques or plaque formation using any monoclonal antibody that binds to an epitope within Aβ1-10 as evidenced by the specification, the limitation of the applicant's working examples to the administration of protein antibody and not nucleic acid encoding an antibody, the lack of specific guidance as to vectors, promoters, routes of vector administration, or nucleic acid sequences encoding antibodies which are capable of treating or preventing amyloid plaque formation or

Alzheimer's disease, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed.

Regarding the previously submitted Koller declaration, the applicant states that the declaratory data provided in the declaration shows that even a brief treatment of antigen wherein antibodies were generated was sufficient to demonstrate clinical benefit. In response, the previous office action stated that the declaratory data relates to clinical trails using the Aβ protein itself and not an antibody or polynucleotide encoding an antibody which recognize Aβ peptide. While the purpose of administering the peptide is to generate antibodies, the mechanism of antibody generation and the nature of the antibodies created are substantially different from applicant's claimed invention which is drawn to administration of nucleic acids encoding the antibodies themselves. Antibodies generated following peptide immunization, a technique referred to as active immunization, are polyclonal and may bind numerous epitopes in the immunizing protein. In the instant invention, nucleic acid encoding a single monoclonal antibody is administered which binds to a specific epitope of the Aβ peptide. Therefore results achieved with polyclonal antibodies are not analogous and not provide a nexus for using any particular monoclonal antibody. Therefore, due to the substantial differences between administration of protein to generate antibodies and the direct administration of antibodies or nucleic acids encoding antibodies, a nexus cannot be found between the applicant's declaratory data and the instant claims as written.

Regarding the previously submitted Arafat et al. reference, the applicant argues that Arafat demonstrates that E1 deleted adenoviral vectors can express therapeutic levels of an antibody. In response, it is reiterated that the Arafat reference is post-filing reference was

published four years after applicant's effective filing date and as such does not demonstrate the state of the art at the time of filing. However, regardless of when Arafat was published, the teachings of the Arafat et al. reference are distinct from the instant invention as claimed. Arafat et al. teaches the intravenous administration of an E1 deleted replication-defective adenovirus encoding a single chain antibody operably linked to a promoter. The single chain antibody disclosed binds to erbB-2 present on tumor cells. Arafat teaches that expression of the single chain antibody following intravenous adenoviral vector delivery resulted in inhibition of tumor growth of tumor cells injected subcutaneously. In contrast, the instant specification does not disclose the use of an E1 deleted replication incompetent adenoviral vector, the sole mention of adenoviruses appears on page 25 of the specification, and is not limited to the use of single chain antibodies. Further, the single chain antibody of Arafat recognizes a antigen present on tumor cells in the periphery and not in the brain. The ability of antibodies to bind to target antigens in the brain is negatively affected by the blood brain barrier which impedes antibody diffusion. In addition, the claims as written are directed to the treatment of diseases associated with amyloid plaques, such as Alzheimer's disease which are substantially different from tumors and cancer. Arafat et al. provides no expectation that the level of antibody in the blood capable of binding to a peripheral tumor following intravenous administration of the E1 deleted adenovirus vector would be capable of entering the brain in sufficient quantity to affect amyloid deposits. Further, Arafat et al. provides no expectation that other vectors, promoter, or routes of delivery would have any therapeutic activity on any disease including cancer. Therefore, in view of the substantial differences between Arafat and the instant invention as claimed, the post-filing date

of the Arafat reference, and the breadth of the claims, the disclosure of Arafat et al. does not support the enablement of the instant specification for the scope of the claims as written.

The office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for claimed methods. Analysis of the combination of factors identified by Wands in light of the teachings of the specification led to the conclusion that the specification fails to provide sufficient guidance to enable the claims as written.

Applicant's amendment has resulted in the following new grounds of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 105-106, 108, 123-124, and 126 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 105 and 123 recite the limitation "the dosages" in claims 93 and 111 respectively. There is insufficient antecedent basis for this limitation in the claim.

Claims 106 and 124 recite the limitation "the intervals between the occasions" in claims 93 and 111 respectively. There is insufficient antecedent basis for this limitation in the claim.

Claims 108 and 126 recite the limitation "the multiple occasions" in claims 93 and 111 respectively. There is insufficient antecedent basis for this limitation in the claim.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the

technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER